Insulin use is associated with poor limb salvage and survival in diabetic patients with chronic limb ischemia

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Objective: **The goal was to compare the outcomes in patients with disabling claudication (DC) or critical limb ischemia (CLI) to determine if diabetics (DM) have poorer patency, limb salvage (LS), and survival rates than nondiabetic patients and if the diabetic regimen affects these outcomes.**

Methods: **All patients who presented with DC or CLI between June 2001 and September 2008 were included. Non-DM patients were compared with those with DM who are currently managed by diet only or oral medications (D-OM), oral medications plus insulin (OM+INS), or insulin alone (INS).**

Results: **Of the 746 patients (886 limbs), there were 406 patients (464 limbs) in non-DM, 96 patients (135 limbs) in D-OM, 98 patients (118 limbs) in OM+INS, and 146 patients (185 limbs) in INS groups. There were more patients with coronary artery disease, hypertension, and renal insufficiency in the DM group than non-DM, with the INS group having the highest incidence of renal insufficiency/dialysis (46%/20%). Gangrene and foot sepsis were significantly more frequent in patients in OM+INS (45%/3%) and INS (50%/6%) than non-DM (15%/0.2%) and D-OM groups (25%/1%; $P < .001$). More patients in the INS group (14%) and OM+INS (9%) had primary amputation than non-DM (4%) and D-OM (4%; $P < .01$). Mean follow-up was 26.3 ± 20.7 months. Overall survival following revascularization was similar in D-OM and non-DM and OM+INS and INS, the latter being significantly worse ($P < .001$). The LS rate in D-OM and non-DM was also identical, whereas OM-INS and INS had significantly worse LS, with OM-INS marginally better than INS ($P = .094$). Primary patency (PP) was worse in endovascular-treated patients on insulin than non-DM and D-OM patients ($P < .001$), whereas PP was similar between groups in open-treated patients. Multivariate analysis showed that coronary artery disease, renal insufficiency, chronic obstructive pulmonary disease, indication for intervention, insulin use, nonambulatory status, and statin drug non-use were independently associated with decreased survival, whereas insulin use, presence of gangrene, need for infrapopliteal interventions, and nonambulatory status were independently associated with limb loss. TransAtlantic Inter-Society Consensus (TASC) classification of the treated lesions being C or D, infrapopliteal interventions, and indication of intervention (DC vs CLI) were independently associated with primary patency, whereas insulin use was not.**

Conclusions: **Diabetic patients who present with limb ischemia can be subdivided into three distinct subgroups based on their diabetic regimen. The survival and LS rates of those controlled with diet or OM are nearly identical to nondiabetics, both of which are significantly better than OM+INS or INS. The PP rate in endovascular-treated patients is worse in patients who are on insulin. Being on insulin is independently associated with decreased survival and limb loss but not PP. (J Vasc Surg 2010;51:1178-89.)**

The incidence of diabetes mellitus (DM) is on the rise, and it is estimated that it will increase by 200% between 2005 and 2050.[1] Since approximately one-quarter of patients with peripheral arterial disease (PAD) have been estimated to have diabetes,[2] an increasingly larger proportion of patients with PAD who undergo revascularization procedures will be diabetic. With the increased use of endovascular interventions for patients with limb ischemia, an endovascular-first approach has been adopted for patients with DM in many specialized centers, including our own.[3-6]

The efficacy of open revascularization in diabetic patients with critical limb ischemia (CLI) has been largely accepted.[7-10] Although there have been large studies which reported similar patency,[9-11] limb salvage,[3,7,12-14] and survival rates[3,10,14] in patients with or without DM following open or endovascular revascularizations, poorer patency,[11-15] limb salvage,[9,11,17] and survival rates[13,17] have also been reported for diabetics. Although patients on insulin were not analyzed separately in most of these studies, its use has been associated with poorer patency,[18] limb salvage,[9,11] and survival[9] rates.

The use of insulin has been associated with increased cardiovascular morbidity and mortality;[19,20] however,

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some have suggested that its use may simply be a marker for the severity of diabetes.[21,22] Few reports on open or endovascular interventions in diabetics have differentiated those requiring insulin for diabetes control and those who did not,[9,11,18] and the conflicting reports may stem from the fact that the patient populations may not be similar in terms of severity of diabetes. The goal of our study was to compare the outcomes in patients with disabling claudication (DC) or CLI to determine if diabetics (DM) have poorer patency, limb salvage (LS), and survival rates than nondiabetic patients and if diabetic regimen affects these outcomes.

MATERIAL AND METHODS

Consecutive patients who presented to the Veterans' Administration Western New York Healthcare System (Buffalo, NY) between June 1, 2001 and September 30, 2008 with chronic limb ischemia (Rutherford category 3-6)[23] and underwent endovascular, open bypass, hybrid revascularization procedures, or primary amputations were prospectively entered into our database. Patients were divided into those with diabetes (DM group) and those without (non-DM group), and the DM group was subgrouped into those whose diabetes was managed by diet or oral medications (D-OM group), a combination of oral medications and insulin (OM+INS group), or by insulin alone (INS group). Demographics, comorbidities, medication usage, clinical presentation, preoperative functional status, noninvasive arterial studies, other imaging studies, TransAtlantic Inter-Society Consensus (TASC) classification,[24,25] details of the procedures performed, the most distal level of intervention, postoperative course, length of stay (LOS), follow-up arterial studies, and status of limbs on last follow-up were recorded.

CLI was defined as the presence of ischemic rest pain for more than two weeks or ischemic tissue loss associated with an absolute ankle pressure less than 50 mm Hg, or toe pressure less than 30 mm Hg. Patients with acute limb ischemia, those with ulcers, and those who had normal arterial circulation with palpable pedal pulses and normal pressures were excluded. Coronary artery disease was defined as documented angina pectoris, myocardial infarction, congestive heart failure, or history of coronary artery revascularization. Renal insufficiency was defined as a serum creatinine level higher than 1.5 mg/dL. Cerebrovascular disease was defined as a history of stroke, transient ischemic attack, carotid artery revascularization, or a known >50% carotid artery stenosis. Hypertension was defined as documented systolic blood pressure of >150 mm Hg, diastolic blood pressure of >90 mm Hg, or pharmacologic treatment with at least one medication. Hypercholesterolemia was defined as fasting cholesterol level >200 mg/dL, low-density lipoprotein level >130 mg/dL, or triglycerides >200 mg/dL, before starting on lipid-lowering drugs. DM was defined as fasting plasma glucose >120 mg/dL, hemoglobin A_{1c}>7%, or treatment with hypoglycemic medications. Amputations were considered major when performed above the ankle level. The original TASC classification was used until 2007,[24] after which TASC II classification[25] was used for iliac and femoropopliteal lesions; however, the original classification was continued to be used for infrapopliteal lesions since the TASC II document did not provide a classification of those lesions.

The decision to proceed with endovascular intervention or open bypass was made by the vascular surgeon, following the diagnostic angiogram, with increasing use of endovascular interventions over the study period. Continuous multilevel occlusions, those with bulky common femoral disease, flush superficial femoral artery (SFA) occlusions, and in patients in whom in-line to the foot was not feasible by endovascular interventions were preferentially treated by open revascularizations. All endovascular procedures were performed by vascular surgeons in the operating room using the OEC 9800 system (General Electric Medical Systems, Salt Lake City, UT). Primary stent placement was used in all iliac lesions. For SFA interventions, TASC A and B lesions were treated using percutaneous transluminal angioplasty (PTA), and stents were used for flow-limiting dissections or residual stenosis or recoil of >30%. Intraluminal crossing was intended for all cases. Most occlusions were crossed using a combination of Glidewire (Terumo, Somerset, NJ) and Glidecath (4 or 5F; Terumo) or QuickCross catheters (Spectranetics, Colorado Springs, Colo). A predilation was followed by stent placement in all SFA occlusions (TASC C and D lesions), whereas PTA alone with provisional stenting was used for popliteal and infrapopliteal occlusions. Debulking procedures were used in a small number of patients (Excimer laser atherectomy; Spectranetics; SilverHawk atherectomy; Foxhollow Inc, Redwood City, Calif).

Patients typically received 5000 U after sheath placement, and the heparin was not reversed at the end of the procedure. Clopidogrel bisulfate was started in the recovery room (300 mg), and was maintained (75 mg daily) for a minimum of 30 days. Lifelong enteric-coated acetyl salicylic acid (ECASA; 81 mg) was also given.

All patients considered for open infrageniculate bypass were evaluated preoperatively by duplex for availability and quality of the greater saphenous veins, with preferential use of ipsilateral greater saphenous veins (GSV). Contralateral GSV or arm veins were used before using synthetic grafts, when ipsilateral GSV was not available or small (<3 mm). Above-the-knee femoropopliteal bypasses (AK-FPB), extra-anatomic bypasses, or aortobifemoral bypasses were preferentially performed using polytetrafluororethylene (PTFE) grafts. Precuffed PTFE grafts were used in patients undergoing infrageniculate bypasses using PTFE grafts. Postoperatively, all patients who had AK-FPB were kept on ECASA, or on clopidogrel when ECASA could not be used. Therapeutic warfarin (International Normalized Ratio kept between 2.0-3.0) was used for below-the-knee PTFE grafts.

Technical success was defined as a patent vessel with <30% residual stenosis. All patients were followed postoperatively, and at three and six months and every six months thereafter for ankle-brachial index (ABI) mea-

Table I. Patients' demographics, comorbidities, and symptoms at presentation

Patients	*Non-DM (n = 406)*	*D-OM (n = 96)*	*OM+INS (n = 146)*	*INS (n = 98)*	P
Age	67.6 ± 10.9	69.6 ± 9.3	71.0 ± 10.3	69.0 ± 10.3	.013[a]
Coronary artery disease	51%	63%	69%	72%	<.001[b]
Hypertension	70%	82%	77%	82%	.009[c]
Cerebrovascular disease	20%	17%	23%	24%	.337
Lipid	70%	69%	76%	67%	.566
Chronic obstructive occlusive disease	28%	27%	21%	17%	.016[d]
Renal	15%	30%	32%	46%	<.001[e]
Dialysis	4%	6%	4%	20%	.002[f]
Active smoker	57%	38%	32%	34%	<.001[g]
Beta-blocker	55%	50%	58%	61%	.265
Angiotensin-converting enzyme inhibitor	43%	61%	58%	58%	<.001[h]
Statin	53%	62%	59%	57%	.203
Nonambulatory	20%	14%	30%	40%	<.001[i]
Limbs	(n = 464)	(n = 119)	(n = 185)	(n = 118)	
Disabling claudication	42%	41%	17%	7%	<.001[j]
Rest pain	25%	10%	5%	7%	<.001[k]
Ulcer	17%	25%	30%	29%	.001[l]
Gangrene	15%	25%	45%	50%	<.001[m]
Foot sepsis	0.2%	1%	3%	6%	<.001[n]

D-OM, Diet-controlled or oral medication-controlled group; *INS,* insulin-only group; *Non-DM,* nondiabetic group; *OM+INS,* oral medication plus insulin-controlled group.

[a]*P* value for non-DM vs OM+INS groups. $P > .05$ for all other group comparisons for age.

[b]Non-DM vs OM+INS, $P = .003$; non-DM vs INS, $P < .001$.

[c]Non-DM vs D-OM, $P = .003$; non-DM vs INS, $P = .003$.

[d]Non-DM vs INS, $P = .047$.

[e]Non-DM vs D-OM, $P = .024$; non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$; D-OM vs INS, $P = .003$; OM+INS vs INS, $P = .085$.

[f]Non-DM vs INS, $P < .001$; D-OM vs INS, $P = .002$; OM+INS vs INS, $P = .002$.

[g]Non-DM vs D-OM, $P = .002$; non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$.

[h]Non-DM vs D-OM, $P = .002$; non-DM vs OM+INS, $P = .013$; non-DM vs INS, $P = .001$.

[i]Non -DM vs OM+INS, $P = .068$; non-DM vs INS, $P = .001$; D-OM vs OM+INS, $P = .013$.

[j]Non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$; D-OM vs OM+INS, $P < .001$; D-OM vs INS, $P < .001$; OM+INS vs INS, $P = .003$.

[k]Non-DM vs D-OM, $P < .001$; non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$.

[l]Non-DM vs D-OM, $P = .068$; non-DM vs OM+INS, $P = .007$; non-DM vs INS, $P < .001$.

[m]Non-DM vs D-OM, $P = .059$; non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$; D-OM vs OM+INS, $P = .001$; D-OM vs INS, $P < .001$.

[n]Non-DM vs OM+INS, $P = .007$; non-DM vs INS, $P < .001$; D-OM vs INS, $P = .019$.

P values for subgroup comparisons are given only if $P < .1$.

Table II. The most distal level of intervention and type of procedures performed in groups based on treated limbs

	Non-DM (n = 445)	*D-OM (n = 114)*	*OM+INS (n = 158)*	*INS (n = 107)*	P
Aortoiliac	40%	25%	17%	7%	<.001[a]
Femoropopliteal	40%	50%	50%	43%	.03[b]
Infrapopliteal	20%	25%	33%	50%	<.001[c]
Multilevel	28%	27%	36%	41%	.005[d]
	(n = 464)	(n = 119)	(n = 185)	(n = 118)	
Open	29%	29%	19%	25%	.133
Endovascular	49%	61%	64%	53%	.009[e]
Hybrid	18%	8%	8%	8%	<.001[f]
PA	4%	4%	9%	14%	<.001[g]

D-OM, Diet-controlled or oral medication-controlled group; *INS,* insulin-only group; *Non-DM,* nondiabetic group; *OM+INS,* oral medication plus insulin-controlled group; *PA*, primary amputation.

[a]Non-DM vs D-OM, $P = .003$; non-DM vs OM+INS, $P < .001$; non-DM vs INS, $P < .001$; D-OM vs INS, $P < .001$; OM+INS vs INS, $P = .006$.

[b]Non-DM vs D-OM, $P = .011$; non-DM vs OM+INS, $P = .008$; D-OM vs INS, $P = .065$; OM+INS vs INS, $P = .006$.

[c]Non-DM vs OM+INS, $P = .021$; non-DM vs INS, $P < .001$; D-OM vs INS, $P < .001$; OM+INS vs INS, $P = .002$.

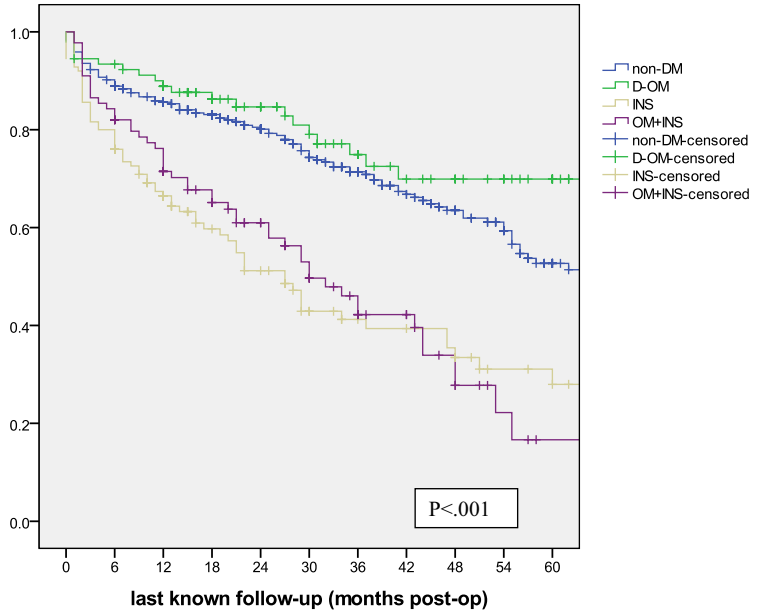
[d]Non-DM vs INS, $P = .003$; D-OM vs OM+INS, $P = .08$; D-OM vs INS, $P = .004$.

[e]Non-DM vs D-OM, $P = .024$; non-DM vs OM+INS, $P = .005$; OM+INS vs INS, $P = .057$.

[f]Non-DM vs D-OM, $P = .007$; non-DM vs OM+INS, $P = .007$; non-DM vs INS, $P = .001$.

[g]Non-DM vs OM+INS, $P = .029$; non-DM vs INS, $P < .001$; D-OM vs INS, $P = .004$.

P values for subgroup comparisons are given only if $P < .1$.



	12 mo	24 mo	36 mo	48 mo	60 mo
Non-DM (n=388)	311	206	138	91	47
D-OM (n=91)	79	51	34	24	15
OM+INS (n=88)	65	41	24	11	1
INS (n=125)	76	41	23	18	10

Fig 1. Overall survival after revascularization. *Non-DM,* nondiabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM and D-OM groups were each significantly better than OM+INS and INS groups ($P < .001$).

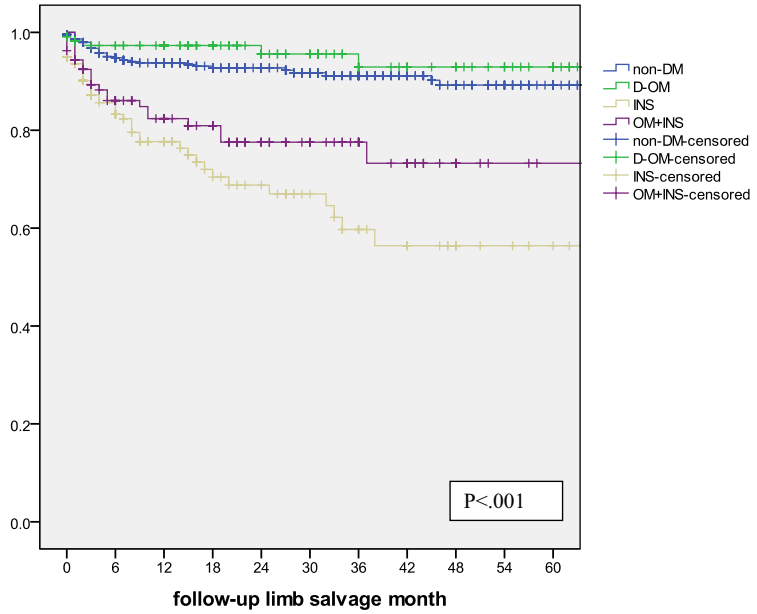
surements, graft or stent velocities, and duplex imaging. We performed repeat angiograms to reassess the adequacy of pedal flow when wound healing was felt to be inadequate, or when duplex suggested restenosis. The loss of patency was defined as occlusion, >50% restenosis, an elevated ratio of velocity to the proximal segment being >3:1 by duplex examination, loss of a previously palpable pulse, or decrease in ABI of >0.2.

Society for Vascular Surgery (SVS) reporting standards for lower extremity arterial procedures were followed.[23] Data analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL). Kaplan-Meier analysis and log-rank test were used to compare groups for primary patency (PP), assisted-primary patency (APP), SP, limb salvage (LS), and overall survival, on an intent-to-treat basis, after excluding patients who had primary amputations. Demographic comparisons were made using two-tailed Fisher's exact test for categorical variables and by *t* test for continuous variables. Multivariate analysis using Cox proportional regression was used to identify the independent predictors of limb loss, patency, and survival. All *P* values were considered significant if <.05. Institutional Review Board approval was obtained for the study.

RESULTS

There were 746 patients (739 males, 886 limbs), of whom 406 patients (464 limbs) were in the non-DM group, 96 patients (135 limbs) in the D-OM group, 98 patients (118 limbs) in the OM+INS group, and 146 patients (185 limbs) in the INS group. Demographics, comorbidities, and presentation modes are shown in Table I. Patients with DM were more likely to have coronary artery disease (CAD), hypertension, renal insufficiency, be on angiotensin-converting enzyme inhibitors (ACEI), and less likely to be active smokers. The INS group were more likely to have renal insufficiency and dialysis dependence than the other groups, whereas patients in OM+INS and INS groups were more likely to be nonambulatory than the D-OM and non-DM groups. There were more patients with foot sepsis in the INS group (6%), and more patients in the insulin-users group had gangrene, whereas claudication and rest pain were more common in the non-DM group.

The most distal level of interventions and the type of interventions are shown in Table II. There were more patients in the INS group who had infrapopliteal interventions, whereas aortoiliac interventions were more common in the non-DM group. More patients in the OM-INS or



	12 mo	24 mo	36 mo	48 mo	60 mo
Non-DM (n=446)	342	213	140	87	46
D-OM (n=114)	97	56	36	26	16
OM+INS (n=107)	76	39	22	12	5
INS (n=158)	66	39	23	9	1

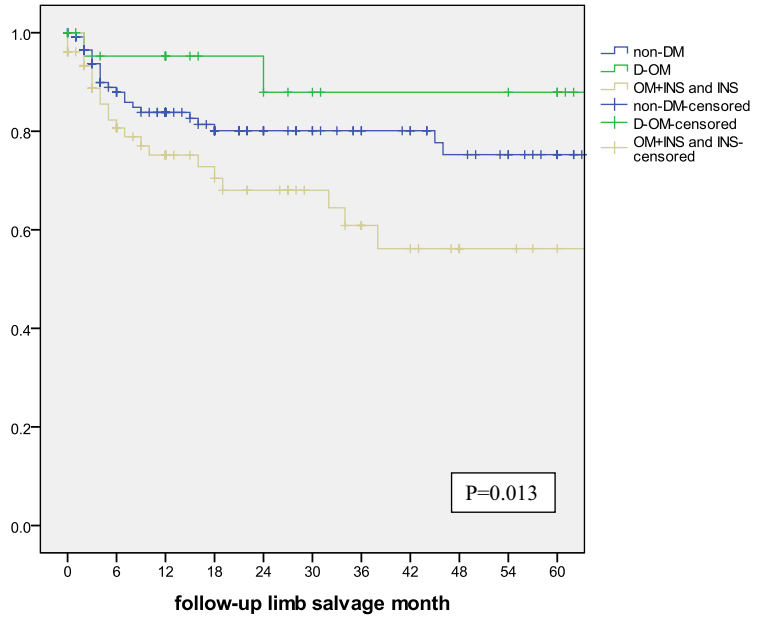
Fig 2. Limb salvage rates in groups after revascularization procedures. *Non-DM,* nondiabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM and D-OM groups were each significantly better than OM+INS and INS groups ($P <$ .001); OM+INS vs INS, $P = .094$.

INS groups underwent multilevel interventions. The majority of endovascular-treated lesions were in the TASC C and D category in all groups, with marginally higher proportion in patients using insulin (non-DM, 59%; D-OM, 65%; OM-INS, 69%; INS, 74% ($P = .06$). More patients in the OM-INS or INS groups had primary amputations (9% in OM-INS and 14% in INS, vs 4% in non-DM and D-OM groups ($P < .001$). Of the patients who underwent infrainguinal bypass procedures (n = 243), 46% (n = 111) were performed with autologous vein grafts (66% [n = 81] for infrapopliteal, 45% [n = 26] for below-knee popliteal, and 7% [n = 4] for above-knee popliteal bypasses).

The 30-day mortality for endovascular-treated patients was 1.8% for non-DM, 0% for D-OM, 1.2% for OM-INS, and 3.0% for INS groups ($P = .968$). The 30-day mortality rate for open treated patients was 3.4% for the whole group, 1.6% for non-DM, 5.8% for D-OM, 3.6% for OM-INS, and 7.0% for the INS groups ($P = .113$). The 30-day mortality in open-treated non-DM patients was not statistically different than DM groups (1.6% vs 5.8%, $P = .1$), and the 30-day mortality in diabetic subgroups was also similar ($P = .727$). The 30-day mortality in the open-treated INS group was marginally worse than the non-DM group (1.6% vs 7.0%, $P = .06$). An additional two patients in the non-DM group (1.1%), one in the OM-INS group (3.6%), and one in the INS group (1.8%) who had open revascularizations had perioperative nonfatal myocardial infarctions.

Mean follow-up was 26.3 ± 20.7 months. The survival rates in non-DM and D-OM groups were very similar (4-year survival 64% ± 3% vs 70% ± 6%), and OM-INS and INS groups were also similar (28% ± 7% vs 34% ± 6%); however, the survival rates in the insulin users were significantly ($P < .001$) worse than those who were not on insulin (Fig 1). When only those with CLI were included, or when the dialysis patients were excluded, the survival between the groups also showed the same pattern, with patients on insulin having significantly lower survival than those in the non-insulin groups.

The LS rates were almost identical in non-DM and D-OM groups (four-year LS rates, 89% ± 2% vs 93% ± 3%), whereas patients in OM-INS (73% ± 6%) and INS groups (56% ± 6%) had significantly worse LS rates than those who were not insulin users, and there was a trend for the



	12 mo	24 mo	36 mo	48 mo	60 mo
Non-DM (n=119)	78	53	41	31	23
D-OM (n=24)	19	13	34	8	7
OM+INS and INS (n=77)	40	25	18	9	4

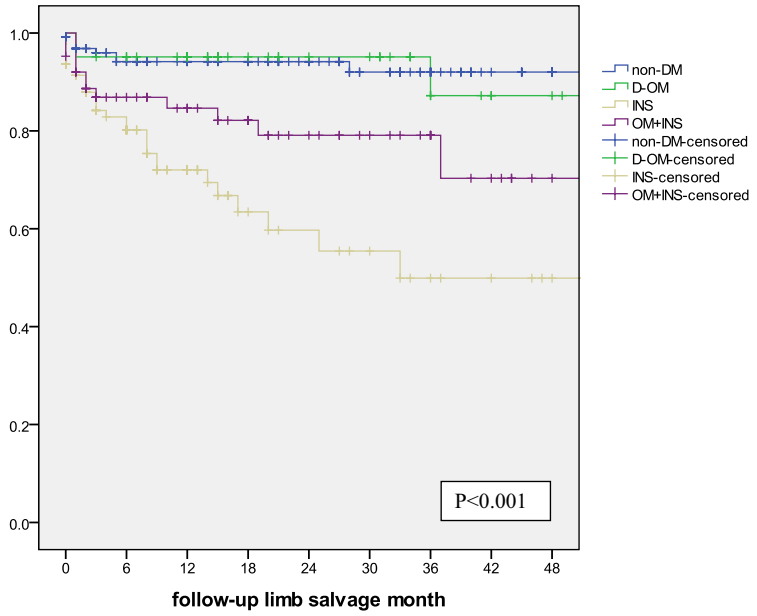
Fig 3. Limb salvage following open revascularization in patients who presented with critical limb ischemia. *Non-DM,* non-diabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM vs D-OM, $P = .244$; D-OM vs OM+INS and INS, $P = .024$; non-DM vs OM+INS and INS, $P = .019$.

OM-INS group to have a better LS rate than the INS groups ($P = .094$; Fig 2). Similar observations were made when only CLI patients were compared, with insulin users having poorer LS than those who were not ($P < .001$); however, the difference between the patients in the OM-INS and INS groups was less pronounced. When dialysis patients were excluded, similar observations were made, with the difference between OM-INS and INS being less pronounced. In CLI patients, LS rates after open revascularizations were worst in insulin users (4-year LS, 56% ± 8%), whereas D-OM (88% ± 6%) and non-DM (75% ± 5%) had better LS rates (Fig 3; $P = .013$). In those who had endovascular interventions, the LS rates were almost identical in non-DM and D-OM groups (four-year LS, 92% ± 3% vs 87% ± 8%), whereas those in the OM-INS and INS groups had significantly worse LS rates (70% ± 9.8% vs 50% ± 9%; $P < .001$; Fig 4). The difference between LS rates in patients with CLI in the OM-INS and INS groups was significant ($P = .042$).

The PP following endovascular interventions was similar between non-DM and D-OM groups (three-year PP, 72% ± 4% vs 78% ± 6%, $P = .989$), which were significantly better ($P < .001$) than OM-INS (60% ± 8%) and INS groups (50% ± 9%; OM-INS vs INS, $P = .193$; Fig 5). The difference was still significant when only CLI patients who had endovascular interventions were compared (two-year PP, 68% ± 5% vs 79% ± 9% vs 55% ± 6%, non-DM vs D-OM vs insulin groups, $P = .02$). The PP was similar in patients who presented with DC on all groups ($P = .510$). The PP was similar following open revascularizations both in patients who presented with CLI ($P = .749$) and with DC ($P = .976$) for all groups.

The SP rates were significantly worse in the INS group than all the other groups (Fig 6; $P = .005$). The SP in claudicants was similar in endovascular-treated patients ($P = .851$). However, SP was significantly better in the D-OM and OM-INS groups than non-DM and INS groups in endovascular-treated patients with CLI ($P = .037$), suggesting that with repeated interventions, a better SP could be achieved in these diabetic groups, whereas the INS group and the non-DM group had worse SP. SP following open revascularizations was similar among all groups ($P = .3$).

In the endovascular-treated patients, 14% had reinterventions (37 endovascular, 1 open) in the diabetic patients to maintain assisted PP, whereas this was 7% (17 endovascular, 2 open) in the nondiabetic patients ($P = .024$), with no difference in the patients with diabetes. Reinterven-



	12 mo	24 mo	36 mo	48 mo
Non-DM (n=129)	90	60	30	10
D-OM (n=41)	34	19	12	6
OM+INS (n=94)	37	22	13	2
INS (n=63)	39	14	7	2

Fig 4. Limb salvage following endovascular revascularization in patients who presented with critical limb ischemia. *Non-DM,* nondiabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM vs OM+INS, $P = .005$; D-OM vs OM+INS, $P = .072$; OM+INS vs INS, $P = .042$; INS vs non-DM, or D-OM, $P < .001$.

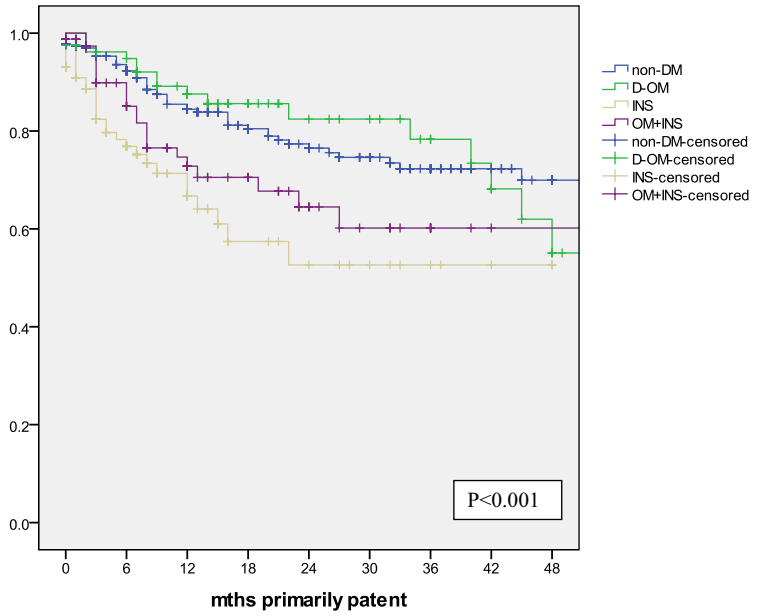
tions after occlusion of the endovascular-treated segments (thrombolysis with or without mechanical thrombectomy, or recanalization of the occluded segment) were performed in 5% of diabetic patients and 4% of nondiabetic patients, with no difference between groups. An open bypass was eventually necessary in 5% of diabetic patients and 4% of nondiabetic patients, with no difference between diabetic subgroups. In the open group, 8% of diabetics and 7% of non-diabetics required interventions to maintain assisted PP, and 8% of the diabetic patients and 12% of the nondiabetic patients required reinterventions after graft occlusion, and there were no differences between groups. Repeat bypass (n = 31) and endovascular recanalizations (n = 5) were performed after graft occlusion in 12% of diabetic patients and 13% of nondiabetic patients, with no difference between groups.

In multivariate analysis using Cox regression, CAD, chronic obstructive pulmonary disease, CLI, renal insufficiency, statin drug nonuse, insulin therapy, and nonambulatory status were found to be associated with decreased survival (Table III). Limb loss was found to be associated with insulin use, in addition to nonambulatory status, infrapopliteal interventions, and the presence of gangrene (Table IV). Poorer PP was found to be associated with infrapopliteal interventions, CLI, and the presence of TASC C or D lesions (Table V). Insulin use, CAD, hypertension, statin use, renal insufficiency, and type of interventions did not correlate with PP.

DISCUSSION

Diabetes remains one of the most important risk factors of peripheral arterial occlusive disease and is present in 25% to 75% of all patients presenting with CLI.[3,5,15-17] The relative incidence of DM in our study population (48%) was well within this range. The optimal management of diabetic patients is still being defined.[11,18,19]

Demographics and clinical presentation. In our series, patients in the INS group were the sickest, with the highest rate of renal insufficiency, dialysis dependence, and nonambulatory status, while the OM+INS group had more patients who were nonambulatory than the D-OM group. All the subgroups in DM group had a higher incidence of CAD, hypertension, and renal insufficiency, but otherwise the D-OM group was similar to the non-DM



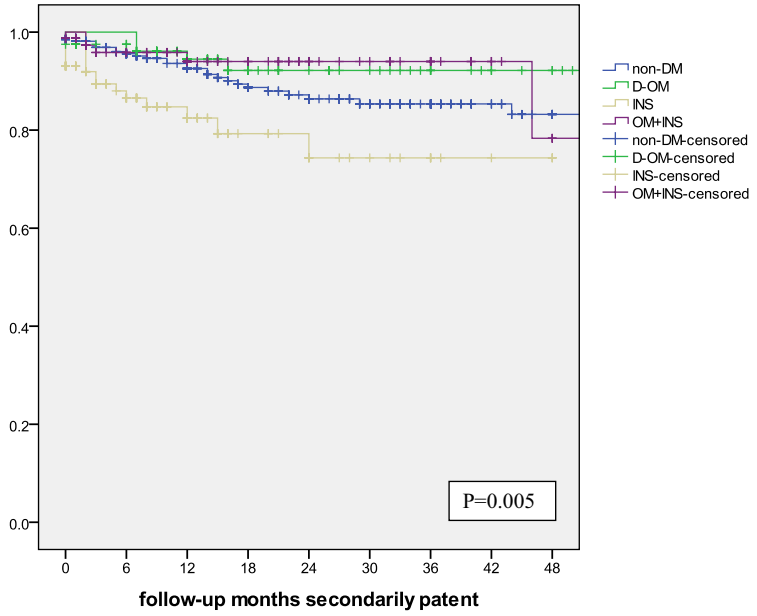
	12 mo	24 mo	36 mo	48 mo
Non-DM (n=267)	167	91	54	27
D-OM (n=80)	56	26	18	9
OM+INS (n=79)	40	18	9	3
INS (n=101)	31	11	5	2

Fig 5. Primary patency following endovascular revascularization. *Non-DM,* nondiabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM vs INS, $P < .001$; D-OM vs INS, $P = .002$; non-DM vs OM+INS, $P = .053$; D-OM vs OM+INS, $P = .068$.

patients. Patients who were using insulin were more likely to present with tissue loss, with or without advanced infection (foot sepsis), with the INS group having the highest rate. The level of intervention was infrapopliteal, and multilevel in more patients on insulin, with the INS group having the highest rate of all groups. All these were reflected by the higher primary amputation rates in insulin users, the highest being in the INS group. These findings all suggest that dividing the patients based on their insulin needs allows a reasonable stratification of diabetic patients when the comorbidities, presentation, and the types of intervention are considered.

Survival. The overall mortality of diabetic patients with chronic limb ischemia in previous reports has ranged from 30% at 1 year[13] to only 42% at 5 years.[10] Patients who received insulin for diabetes were also shown to have an increased rate of cardiovascular events and mortality.[19,20] In our study, insulin use was found to be independently associated with decreased survival, with the survival of noninsulin-dependent diabetic patients identical to nondiabetics (50%-70% at five years), and survival in the insulin subgroups was also very similar (17%-28% at five years); both significantly less than the non-insulin users. We found similar results when we compared only those who presented with CLI.

Limb salvage. The effect of diabetes on limb salvage rates has been conflicting, regardless of the revascularization technique employed. DeRubertis et al[12] reported 88% one-year LS rates in patients with or without DM following percutaneous interventions, and although the PP rate was less in the DM group, they concluded that this was likely due to having a higher proportion of CLI in diabetic patients, and, with repeated interventions, similar patency and limb salvage rates were achieved. In contrast, Bakken et al[11] found significantly lower LS rates in diabetics (one-year LS rate was 67% in noninsulin-dependent diabetics and 73% in insulin-dependent diabetics, whereas it was 89% in nondiabetics) who had SFA endovascular interventions with no difference in patency. Other series have reported 75% to 91% LS rates one year following endovascular interventions.[13,18,26-28] Dick et al[13] reported that patients with DM had similar LS at one year with nondiabetics, and whether the initial treatment was open or endovascular did not have any effect on these outcomes. As for the open



	12 mo	24 mo	36 mo	48 mo
Non-DM (n=267)	182	107	63	12
D-OM (n=80)	59	30	20	12
OM+INS (n=79)	52	27	16	6
INS (n=101)	37	16	7	2

Fig 6. Secondary patency following endovascular revascularization. *Non-DM,* nondiabetic group; *D-OM,* diet-controlled or oral medication-controlled group; *OM+INS,* oral medication plus insulin-controlled group; *INS,* insulin-only group. Non-DM vs INS, $P = .007$; D-OM vs INS, $P = .009$; OM+INS vs INS, $P = .013$; non-DM vs D-OM or OM+INS, $P =$ NS.

bypasses, some reports suggested similar LS rates following bypass procedures,[3,7,10] whereas others noted lower LS rates.[29,30] Akbari et al[10] reported a five-year LS rate of 87% following infrainguinal vein bypasses, with a five-year survival rate of 58%, both similar to their nondiabetic patients. In our study, patients in the D-OM group had identical LS rates with nondiabetics, both of which were significantly better than the insulin users. This was similar when only CLI patients were included, and the OM+INS group had slightly better LS rates than the INS group, but this did not reach statistical significance. The LS rates in the insulin groups were worse than in the noninsulin users both in the open and endovascular-treated patients with CLI; however, the difference between the OM+INS and INS groups was also different in endovascular-treated patients. Of note, the LS rate in our D-OM group (four-year LS 87% for endovascular, 88% for open groups) was close to that reported by Akbari et al,[10] although their series included only patients with autologous vein reconstructions.

Patency. Patency rates have also been reported to differ in diabetics following endovascular and open reconstructions, based on the indication for intervention. Bakken et al[11] found that the insulin-dependent diabetics had worse PP and APP than nondiabetics and noninsulin-dependent diabetics following percutaneous SFA interventions for claudication but similar patency rates to CLI patients. Others[12,13] have reported that diabetic patients with CLI have higher restenosis and reintervention rates, but comparable limb salvage rates can be achieved. We found similar PP rates in the diabetic subgroups following both endovascular and open procedures in claudicants and those with CLI who underwent open bypasses. However, PP was different in patients who presented with CLI and had endovascular interventions, with insulin users having the worst outcomes. The SP rates were also worse in the endovascular-treated patients on insulin with CLI. Multivariate analysis showed that CLI, TASC classification C or D, and need for infrapopliteal interventions were associated with worse patency rates, whereas insulin use and the type of procedure were not. Our poorer results in insulin users may be a reflection that patients who are on insulin had more complex anatomy and worse clinical presentation.

The effect of hyperglycemia, insulin resistance, and DM on endothelium and the vascular system has been exten-

Table III. Multivariate analysis (Cox regression) for survival

	Hazard ratio	*95% Confidence interval*	P
Coronary artery disease	1.8	1.4-2.4	<.001
Chronic obstructive occlusive disease	1.5	1.2-1.9	.002
Renal	1.9	1.4-2.4	<.001
Statin nonuse	1.4	1.1-1.8	.004
Indication	2.3	1.6-3.3	<.001
Insulin	1.5	1.1-1.9	.003
Nonambulatory	1.9	1.5-2.5	<.001

Table IV. Multivariate analysis (Cox regression) for limb salvage

	Hazard ratio	*95% Confidence interval*	P
Insulin	2.4	1.5-3.6	<.001
Nonambulatory	1.9	1.3-2.9	.002
Infrapopliteal	3.3	2.2-5.2	<.001
Gangrene	2.3	1.3-2.9	<.001

Table V. Multivariate analysis (Cox regression) for primary patency

	Hazard ratio	*95% Confidence interval*	P
Infrapopliteal	1.8	1.4-1.9	<.001
DC/CLI	1.5	1.1-2.1	.021
TASC C/D	2.1	1.3-3.3	.002

CLI, Critical limb ischemia; *DC,* disabling claudication; *TASC,* TransAtlantic Society Consensus.

sively studied.[31] Insulin stimulates the production of NO[32] and increases endothelium-derived NO synthase expression,[33] while glucose inhibits the production of NO[34] along with prostaglangin I_2.[35] Elevated glucose and insulin levels are associated with an increased secretion of the vasoconstrictor, endothelin-1, and impaired glucose tolerance increases arterial stiffness.[36] Serum insulin and C-peptide levels have been suggested to be associated with restenosis following percutaneous angioplasties in claudicants and CLI patients.[37] Although it is not clear if the effects of insulin are primarily correlated with worsening of atherosclerotic disease or if it is simply a marker of more severe disease[21,22] and how much of its glycemic control counteracts its direct effects on the vascular system, our results suggest that subdividing the diabetic patients into groups based on their insulin need is reasonable and allows better stratification of patients.

The main weakness of our study is the retrospective nature and lack of randomization. It is almost exclusively composed of men, and our findings may not be applicable to female patients. All the patients were subgrouped for their medication status at the time of presentation. Thus, patients crossing over to other groups during the study would not have been identified during follow-up. We also did not document the duration of DM, monitor the compliance of the patients with glucose control, and did not monitor HbA1c levels.

CONCLUSIONS

Diabetic patients who present with limb ischemia can be divided into three distinct subgroups based on their diabetic regimen, with different presentation and treatment modes, and LS and survival. The survival and LS rates of those controlled with diet or OM are nearly identical to nondiabetics. The PP rate in EV-treated patients is worse in patients who are on insulin. Insulin usage is independently associated with decreased survival and limb loss but not patency. Studies comparing DM with non-DM should definitely specify insulin use, with or without combination with oral medications.

AUTHOR CONTRIBUTIONS

Conception and design: HD
Analysis and interpretation: HD, PL, NN, LH, MD
Data collection: HD
Writing the article: HD
Critical revision of the article: HD, PL, NN, LH, MD
Final approval of the article: HD, PL, NN, LH, MD
Statistical analysis: HD, NN
Obtained funding: N/A
Overall responsibility: HD

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DISCUSSION

Dr Theodore Teruya (*Loma Linda, Calif*). The authors found that patients who use insulin as either monotherapy or in combination with oral hypoglycemic agents had worse limb salvage and survival.

It is well known that tight glycemic control can limit the complications of diabetes. Did the authors measure hemoglobin A1c levels and, if so, were they significantly different in the groups with diabetes? Was the use of insulin just a marker of poor glycemic control?

We also know that the most frequent cause of limb loss in diabetics is due to pedal sepsis and not critical limb ischemia. How many patients suffered limb loss due to overwhelming infections or extensive tissue loss? Our group at Loma Linda presented a manuscript here at this meeting in 2002 that showed that 24% of major amputations performed were from pedal sepsis or extensive tissue loss.

Finally, what was the rationale for including patients without critical limb ischemia (ie, the claudication group) in this study? There were more claudicants in the nondiabetic and oral hypoglycemic agent groups, than in the groups that took insulin. Do you think this affected the outcome of the study?

Dr Dosluoglu. This is a retrospective study, and that's the weakness of the study. I tried to see if the patients did have data on hemoglobin A1c levels. It was really not very reliably found. So I'm not going to be able to give you any data on the tight control vs long-term or short-term on this subgroup, but I agree with you.

Another aspect of this is that hemoglobin A1c actually could be a reflection of other end products of poor diabetes control as well, so we are planning on prospectively evaluating this in the future. I truly believe though this may be not only tight control, but it is a reflection of the level of diabetes affecting the outcomes.

As to the last question, we did include the diabetics and claudicants to see if there were patency differences, as was suggested by the University of Rochester paper. I actually analyzed them separately so that we could actually iron that out in terms of outcomes.

Lastly, the infection-related amputations were clearly more common in the insulin group than others. I looked at it also; it was about 50% of the patients who had infection-related amputation. We just recently wrote a paper, which was published in the June issue of the Journal, on the limb loss with patent endovascular-treated segments, in which we observed that a lot of the amputations occurred in patients with patent stents, which is a reflection of our aggressiveness in that we try to save these limbs, and we lose some due to infections. It may be related to poor glucose control, but I do not have the specific data for that.

Dr Jonathan Eliason (*Ann Arbor, Mich*). Was there any consideration to look at the type of insulin control that patients had: long-acting, sliding-scale–based, older formulations, or newer formulations, and whether or not there is a difference? I know it's tough to tease those out.

Dr Dosluoglu. It could be done. That's easier than getting the hemoglobin A1c, because hemoglobin A1c was not necessarily obtained in a lot of these, so I cannot really get that. Due to the large number of patients, this would require a lot of effort, and we elected not to do that for this study.